specification. If the Examiner should disagree, he is respectfully requested to point out the contested limitation with particularity in the next Office Action so Applicants can cite specific support in response thereto. Kindly note that amendments and cancellations of claims are made without prejudice to prosecution of the original subject matter in the future.

In response to a restriction requirement by the Examiner, Applicants elected with traverse the claims of Group I. Claims 1-6, 8-23, 25-35 and 39 have been examined on the merits as they relate to use of the invention in animals or cells thereof. Claims 7, 24 and 36-38 have been withdrawn from consideration by the Examiner "as being drawn to a nonelected invention, there being no allowable generic or linking claim." The latter statement found on page 3 of Paper No. 12 is understood by Applicants to mean that examination will be extended to nonanimal organisms and cells after a generic claim is found to be allowable by the Examiner. If Applicants' inference is incorrect, clarification by the Examiner is requested.

Applicants do not agree with the statements made on page 2 of Paper No. 12. There is no factual basis provided by the Examiner for concluding, "The success of the method of using dsRNA to inhibit gene expression is subject to a variety of cellular factors that include the origin of the cell." Applicants teach a variety of methods to provide RNA in a cell on pages 13-14 of the specification. But no evidence or reasoning is presented in Paper No. 12 to substantiate the Examiner's conclusion that differences between animal and plant cells "may affect success of the claimed method." Finally, the evidence of record (e.g., Waterhouse et al., Proc. Natl. Acad. Sci. USA, 95, 13959-13964; Chuang et al., Proc. Natl. Acad. Sci. USA, 97, 4985-4990) shows that the success of the claimed invention in animals is predictive of success in plants when Applicants' disclosure is followed. Applicants predicted the generality of using dsRNA to inhibit gene expression in plants and

animals in their provisional application filed in 1997, and the references published after their priority date (and discussed below) prove the accuracy of that prediction.

35 U.S.C. 112 – Definiteness

Claims 1-6, 8-23, 25-35 and 39 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claims 1, 22 and 39 have been amended to clarify that the portion of the target gene is at least 25 bases in length. This amendment is supported by page 11, lines 27-28, of the specification (cf. original claims 10 and 28). The Examiner's suggestions for correcting claims 12 and 35 have been adopted. These amendments address informalities and do not change the original scope of the claims.

Applicants submit that the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

The written description requirement must communicate that which is needed to enable the skilled artisan to make and use the claimed invention. *Kennecott v. Kyocera Int'l*, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987). Inquiry into satisfaction of the written description requirement is factual and depends on the nature of the invention and the amount of knowledge imparted by the disclosure to those skilled in the art. See *Staehelin v. Secher*, 24 USPQ2d 1513, 1519 (B.P.A.I. 1992)

Claim 1-6, 8-23, 25-35 and 39 were rejected under Section 112, first paragraph, because they allegedly contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because the nature of the claimed invention and the amount of knowledge imparted on the skilled artisan by their teachings show that the written description requirement has been satisfied by this specification.

Applicants' specification provides extensive teachings to show that they had possession of the full scope of the claimed invention. For example, various target genes are described from page 16, line 20, to page 17, line 8, of the specification; similarly, different organisms are described on page 12, lines 3-30, of the specification. Page 18, line 20-21, of the specification notes that nucleotide sequences of the yeast, *D. melanogaster*, and *C. elegans* genomes were available. Unlike the case in which a rat insulin cDNA did not provide an adequate written description of insulin cDNA from other mammals because members of the genus were merely named by their function (i.e., hormone activity), see *Univ. of Calif. v. Eli Lilly*, 43 USPQ2d 1398 (Fed. Cir. 1997), here the target genes and organisms named in the specification were available to Applicants as well as the public at the time of filing. Moreover, the Examiner has not specified any technical limitation that would prevent a skilled artisan from practicing the claimed invention with a variety of target genes and organisms. Thus, the listing in Applicants' specification of target genes of known sequences and organisms which were publicly available by their names does satisfy the written description requirement for use of the claimed invention outside the scope of the target genes and organism used in the working examples.

In contradiction to the repeated assertions in Paper No. 20 that only a limited number of genes was exemplified, Applicants actually provided examples of specific dsRNA-mediated inhibition for nine different genes in *C. elegans* (see Examples on pages 23-40 of the specification). Seven of these genes are present naturally in the genome of *C. elegans* (i.e., they are endogenous genes): unc-22, fem-1, unc-54,

hlh-1, pos-1, sqt-3, and mex-3. In each case, introduction of dsRNA into cells of the animal produced phenotypes which indicated that expression of the target gene was inhibited. Inhibition of two different exogenous genes (i.e., gfp and lacZ transgenes) was also demonstrated. For three of the endogenous genes (i.e., unc-22, unc-54, and hlh-1), examples were provided showing that two distinct (i.e., nonoverlapping) segments of dsRNA corresponding to different regions of the target messenger RNA each yielded a specific loss of function phenotype for the endogenous gene.

As stated by the court, "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). Here, the use of particular target genes from *C. elegans* is merely illustrative of Applicants' invention and is not meant to be limiting. A large number of genes from many different organisms are known. Techniques for the manipulation of genes, the introduction of RNA into cells (e.g., by microinjection or feeding), the production of RNA by expression vectors within cells, and the measurement of gene expression are described in Applicants' specification. Other techniques for introduction of RNA into a cell or organism, transfection of expression constructs, and the production of transgenic animals and plants that stably inherit and express the transgene are also known. No technical deficiency in the disclosure of Applicants' specification is cited in Paper No. 20 that would lead the skilled artisan to conclude that the claimed invention could not be practiced commensurate in scope with the disclosure.

As disclosed by Applicants in their specification, the claimed invention is not limited to particular target genes or organisms. Moreover, the evidence of record shows the general applicability of the claimed invention to target genes and organisms other than those exemplified in Applicants' specification. It should be noted by the Examiner that many of the references made of record by submission of information disclosure statements cite Applicants for the description of the method for

inhibition of gene expression used in their studies (e.g., "as described by Fire et al., 1998"). Although such examples are not part of this specification, they are evidence that undue experimentation was not required for others to practice the claimed invention with a variety of target genes and organisms when Applicants' disclosure was followed. This fact will be further discussed below in the response to the enablement rejection.

Furthermore, as is legally accepted in patent law, Applicants' specification and their specific examples do not limit the legal protection provided by the claims (e.g., "Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications can be practiced. Therefore the foregoing descriptions and examples should not be construed as limiting the scope of the invention, which is delineated by the appended claims." col. 20, lines 40-46, of U.S. Patent No. 6,136,601). This explanation was also stated on page 23, lines 9-10, and page 40, lines 21-29, of Applicants' specification.

It is speculated on page 6 of Paper No. 12, "The success of the claimed methods varies from gene to gene and from organism to organism." No evidence, however, is cited to support this assertion. There are further statements that the "structure" or "accessibility" would determine the success of the claimed invention, but again no evidence is provided to support such assertions. Thus, Applicants submit that the reasons provided in Paper No. 12 to show that the use of the claimed invention is limited to the exemplified target genes and *C. elegans* are merely speculative and do not reflect the evidence of record.

Therefore, although the working examples in the specification are directed to a variety of target genes in *C. elegans*, it is submitted that the constructive reduction to practice of other embodiments of the claimed invention using the target genes

and organisms listed in the specification (and available to the public as of the filing date) satisfies the written description requirement of Section 112, first paragraph.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04 and cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *in re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons to justify an enablement rejection are always required. See M.P.E.P. § 2164.04.

Claim 1-6, 8-23, 25-35 and 39 were rejected under Section 112, first paragraph, because the specification allegedly "does not reasonably provide enablement for a method or kit to inhibit expression of any target gene in any cell." Applicants traverse because their specification enables the skilled artisan to make and use the claimed invention.

As discussed above, Applicants' specification on pages 12 and 16-17 teaches using other organisms and other target genes beside those taught in their working examples. The working examples in this application show that the practice of the claimed invention is not limited to particular types of target genes or portions of their nucleotide sequences.

The Examiner appears to require actual reduction to practice of the claimed invention for organisms other than *C. elegans* prior to the filing date of the application. But it is well established that an extensive number of working examples are not required to provide an enabling disclosure. While such examples may provide addi-

tional useful information, persons having the knowledge of a skilled artisan could practice the invention without the exercise of an undue amount of experimentation using Applicants' disclosure. See *Ex parte Nardi*, 229 USPQ 79, 80 (B.P.A.I. 1986).

The initial evidence for the generality of the claimed invention came from the work published by Applicants on additional target genes in *C. elegans* (see their references submitted in the information disclosure statements). These publications and the interest they elicited from the others in the scientific community led to work that demonstrated that the predictions made in this application for the general applicability of the claimed invention to a variety of target genes and organisms are correct. References made of record have shown that gene expression can be inhibited by the method of the claimed invention in a variety of organisms such as plants, drosophila, other insects, cnidaria, planaria, leeches, protozoa, amphibians, hamsters, and mice or cells thereof. Of particular interest is the use of the claimed invention with organisms in which classical genetics and associated techniques (e.g., homologous recombination) have not been developed. The review by Hunter (Curr. Biol., 10, R137-R140) confirms Applicants' predictions that the claimed invention is generally applicable by stating that the mechanism by which dsRNA inhibits gene expression is conserved and ancient.

The concern that inhibition of gfp expression may not occur in some cells (e.g., certain muscle cells as described on page 31, lines 10-22, of the specification) does not indicate that the expression of other target genes in those same cells cannot be inhibited by the claimed invention.

It is an oversimplification to contend that any technique, even those that are widely used and well known in the art, will be effective under all conditions. Inoperative embodiments falling within the scope of the claims are not an adequate basis for concluding that undue experimentation is required. *In re Angstadt*, 190 USPQ 214,

218-219 (C.C.P.A. 1976). Three examples are discussed here to illustrate the incorrectness of contentions in Paper No. 12 that applicants for a patent are required to show that all genes and all organisms could be effectively used in the claimed invention (copies of the patents and publications cited in this paragraph can be provided at the Examiner's request). (1) PCR is a general technique for amplifying nucleotide sequences (see U.S. Patent No. 4,683,195), but false positive and false negative results can be obtained. In some cases, this is due to the incompatibility of the sequence of the target gene with the conditions of the PCR reaction. A discussion of limitations of PCR can be found in Burkardt (Clin. Chem. Lab. Med., 38, 87-91). (2) Lipofection is a general technique for transfecting cell lines (see U.S. Patent No. 4,897,355), but some cell lines are recalcitrant to the effects of such lipids (see Van Tendeloo et al., Gene Therapy, 5, 700-707). (3) Monoclonal antibodies can be used to produce reagents that specifically bind to antigens of interest (see U.S. Patent No. 4,350,683), but some proteins are poor immunogens (see Harlow et al., *Antibodies – A Laboratory Manual*, page 57, CSHL Press) or cannot be used to raise antibodies for other reasons. Despite this limitation, monoclonal antibodies are a useful tool. Note that generation of monoclonal antibodies from a known antigen does not involve undue experimentation. See *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Finally it should be noted that if a particular target gene is not amenable to inhibition by the claimed invention, the identification of such genes would not involve undue experimentation because producing a dsRNA, introduction of dsRNA into a cell, and determination of inhibition are routine for the skilled artisan. With respect to the concern that there are certain structural features or portions of the sequence of target genes that are critical for operability of the invention, there is no evidence provided in Paper No. 20 to support the Examiner's assertion that such structures or

sequences are critical. Recent work (Parrish et al., Molecular Cell, 6, 1077-1087) confirms Applicants' prediction that dsRNA-mediated inhibition is generally applicable by showing that any region of the gfp transcript can be used to produce dsRNA and suggesting that choice of dsRNA segments to inhibit the unc-22 gene is similarly flexible. Of course there are some circumstances such as, for example, one dsRNA intended to inhibit the unc-22 gene which is not effective (Parrish et al., *id.*) and results in zebrafish are equivocal (Wargelius et al., Biochem. Biophys. Res. Comm., 263, 156-161; Li et al., Dev. Biol., 217, 394-405; Oates et al., Dev. Biol., 224, 20-28).

Therefore, the specification enables a skilled artisan to make and use the claimed invention commensurate in scope with the broad disclosure. Applicants' teachings enable others to practice the claimed invention without undue experimentation. This is shown by the wide acceptance of dsRNA-mediated inhibition and its use by the scientific community with a variety of target genes and organisms in a short period after Applicants' disclosure of their work. Such evidence of wide and rapid acceptance is indicative that undue experimentation was not required, and shows that the enablement requirement of Section 112, first paragraph, has been satisfied. In contrast, antisense inhibition in organisms other than bacteria required undue experimentation and this was borne out by the results of post-filing experiments. See *Enzo Biochem v. Calgene*, 52 USPQ2d 1129, 1137 (Fed. Cir. 1999). Here, the weight of post-filing attempts to use the claimed invention were successful and citation of Fire et al. (Nature, 391, 806-811) in those publications for the method used to inhibit a variety of target genes in plants, animals, and protozoa shows that the authors followed Applicants' enabling disclosure. Cf. *Johns Hopkins Univ. v. Cellpro*, 47 USPQ2d 1705, 1718 (Fed. Cir. 1998).

For the above reasons, withdrawal of the rejections under Section 112 is respectfully requested.

Applicants have phoned Examiner Nikodem to arrange for an interview. The Examiner indicated that he would soon be leaving the Office and that it would be better to have the interview with the examiner who would be assigned responsibility for this application. In a subsequent telephone conversation with Supervisory Prirnary Examiner Deborah Clark, she indicated that a new examiner would be assigned after this Amendment had been received. Therefore, after the Examiner has considered the amendments and arguments made herein and prior to issuing an Office Action, Applicants respectfully request that a personal interview be scheduled with the undersigned.

Having responded to all of the objections and rejections in the Office Action (Paper No. 12) mailed June 2, 2000, Applicants submit that the pending claims are in condition for allowance and an early Notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned if further information is required.

Respectfully submitted,

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